REMARKS

Amendments

Withdrawn claims 27-33 and 38-50, drawn to compositions and combinations, are cancelled. Claim 11 is amended to recite specific the multidrug resistance reversing agents and biological response modifiers recited in claims 15-18. Claims 15-18 are amended to delete unnecessary language.

Objection to the Specification

The blank section on page 12 is due to electronic formatting. No text is missing. Withdrawal of the objection is respectfully requested.

Rejection under 35 USC §112, first paragraph

Claims 14, 16, and 17 are rejected as allegedly failing to provide written description of the claimed subject matter. This rejection is traversed.

In the rejection it is alleged that there is insufficient "written description" for the terms "multidrug resistance reversing agents," and "biological response modifiers." While applicants disagree with this assertion, claim 14 is cancelled and claims 16 is amended to delete the term "biological response modifiers," thus rendering the rejection moot. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC §103(a) in view of Chu et al.

Claims 11-14, 16, 17, 19-21, 23-26, 34, 35, and 37 are rejected as allegedly being obvious in view of Chu et al. (WO 96/07413). This rejection is traversed.

At page 6, lines 18-28, WO '413 discloses that (-)-(2S, 4S)-1-(2-hydroxymethyl-1,3-dioxolan-4-yl) cytosine, also known as (-)-OddC, has activity against cancer cells. Thereafter, WO '413 lists general examples of such cancers including lung, breast, bladder, pancreas, lymphoma and leukemia.

At page 7, line 30- page 8, line 11, WO '413 discloses that the compounds described therein can be administered in combination or alternation with other anti-tumor agents. WO '413 provides a long list of specific agents including, among others, nitrogen mustards,

ethyleneimine compounds, alkyl sulfates, growth factors, and growth factors, as well as alpha, beta, and gamma interferons and interleukin. As a specific combination, WO '413 describe the combination of (-)-OddC and THU, i.e., tetrahydrouridine, a cytidine deaminase inhibitor. See page 8, lines 22-29. WO '413 does not include cytarabine in its long list of agents at page 7, line 30- page 8, line 11.

As mentioned, at page 4, lines 3-16 of WO '413 (see also page 37, lines , cytarabine (or cytosine arabinoside or araC) is a cytosine nucleoside analog used in the treatment of acute myeloid leukemia, and has activity "against acute lymphocytic leukemia, and to a lesser extent, is useful in chronic myelocytic leukemia and non-Hodgkin's lymphoma." It is noted that the compounds of applicants' formula I are also cytosine nucleoside analogs.

Additionally, the rejection refers to the data presented at page 40 of WO '413 and argues that (-)-L-OddC is more potent that cytarabine against the CEM line. It is noted that the data shown a difference of only 0.005 μM with a margin of error of ± 0.01 for the cytarabine data and a margin of error of ± 0.03 for the (-)-L-OddC data.

In light of this disclosure in WO '413, it is asserted that it would be obvious to combine β-L-OddC with cytarabine to treat leukemia. However, it is respectfully submitted that the rejection fails to establish sufficient motivation that would lead one of ordinary skill in the art, in light of the disclosure of WO '413, to an embodiment in accordance with Applicants' claimed invention.

For example, the rejection fails to set forth the motivation that would lead one of ordinary skill in the art to first select leukemia from the long list of possible tumors or possible cancers presented at page 6 of the WO '413 disclosure and then further select cytarabine to be used in combination with β-L-OddC. It is noted that cytarabine is not even listed in the long list of anti-tumor agents presented in the paragraph bridging pages 7 and 8 of WO '413. There is no motivation set forth as to why one of ordinary skill in the art would go beyond this list of anti-tumor agents and combine another agent with β-L-OddC.

Furthermore, if the impetus for combining two agents is to achieve a broader spectrum of activity, the rejection fails to indicate why one would combine cytosine nucleoside analog with another cytosine nucleoside analog. Moreover, the rejection fails to set forth any motivation as to why one would combine three agents together in a method of treatment.

The mere ability to modify the disclosure of a reference does not, in and of itself,

establish obviousness. Instead, the rejection must set forth a sufficient motivation that would lead one of ordinary skill in the art to make such a modification so as to arrive in an embodiment of a claimed invention. Here, no motivation is presented.

The rejection merely alleges that it would be obvious to use two cancer treatment agents together. But, there is no motivation presented as to why one would (1) select leukemia, as the cancer to be treated, (2) further select an agent such as an interleukin, from a long list of specific anti-tumor agents encompassing a large number of diverse compounds, as an anti-tumor agent to be used in combination with β-L-OddC, and then further select a third agent to be used in combination with the other two, particularly when that third agent is not mentioned in the long list of specific anti-tumor agents disclosed, and which like β-L-OddC is a cytosine nucleoside analog. The first case cited by the Examiner, *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), dealt with a detergent composition and a combination of components known for use in detergents. The second case cited by the Examiner, *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980), dealt with a method for treating iron prior to casting and a combination of two agents each known for promoting formation of iron nodular structure in iron. Neither case dealt with a combination of agents administered internally, let alone a combination of agents for treating a disease, let alone a combination of agents for treating cancer.

Additionally, in Example 11, WO '413 asserts that (-)-OddC was evaluated in NCI's cancer screening program. As shown in Table 2 at page 35, the leukemia cell lines are identified as CCRF-CEM, RL-60(TB), K-562, BSOL T-4, RPMI-2.26, and SR. Applicants' have attempted to find out the identities of the cell lines, some of which are apparently incorrectly named by Chu et al. CCRF-CEM is an acute lymphoblastic cell line. It is believed that RL-60(TB) was intended to be HL-60, which is an acute promyelocytic leukemia cell line. K-562 is a chronic myelogenous leukemia (CML) cell line. It is believed that BSOLT-4 was intended to be MOLT-4, an acute lymphoblastic leukemia cell line. RPMI-2.26 is assumed to be a reference to RPMI-82.26, a human hematopoietic cell line obtained from a patient with multiple myeloma. Finally, SR is a B-lymphoblastoid cell line. See also the Examiner's footnote at the bottom of page 7 of the Office Action.

Thus, none of these cell lines mentioned in Example 11 appear to be an acute myelogenous leukemia cell line. As a result, WO '413 provides no disclosure or suggestion

that the compound, (-)-OddC is suitable for treating acute myelogenous leukemia. Nor does WO '413 suggests using applicants' claimed combination for treating acute myelogenous leukemia. Compare claim 13.

In view of the above remarks, it is respectfully submitted that WO '413 fails to establish sufficient motivation which would lead one of ordinary skill in the art to modify the disclosure of WO '413 in such a manner as to arrive at an embodiment in accordance with Applicants' claimed invention. Withdrawal of the rejection under 35 U.S.C. § 103 is respectfully requested.

Rejection under 35 USC §103(a) in view of Chu et al., Advani et al. and Jamkubowski et al.

Claims 11-21, 23-26, 34, 35, and 37 are rejected as allegedly being obvious in view of Chu et al. (WO 96/07413) in combination with the article by Advani et al. and the article by Jamkubowski et al. This rejection is traversed.

In the rejection, it is argued that the article by Advani et al. discloses that PSC 833 has been used clinically for treating poor-risk AML (acute myelogenous leukemia). Such disclosure provides no suggestion for modifying the disclosure of WO '413 since, as discussed above, WO '413 provides no disclosure or suggestion that the compound, (-)-OddC, is suitable for treating acute myelogenous leukemia. Moreover, Advani et al. provide no suggestion of combining (-)-OddC with PSC 833.

Similarly, in the rejection it is asserted that the article by Jamkubowski et al. discloses treating AML with granulocyte colony-stimulating factor. Such disclosure provides no suggestion for modifying the disclosure of WO '413 since the latter provides no disclosure or suggestion that the compound, (-)-OddC is suitable for treating acute myelogenous leukemia. Moreover, Jamkubowski et al. provide no suggestion of combining (-)-OddC with granulocyte colony-stimulating factor.

It is respectfully submitted that neither Advani et al. nor Jamkubowski et al. overcome the deficiencies discussed above with regards to the rejection in view of WO '413 alone. Furthermore, neither Advani et al. nor Jamkubowski et al. provide any motivation to modify the disclosure of WO '413 such as to arrive at an embodiment in accordance with applicants' claimed method. Withdrawal of the rejection is respectfully requested.

Rejection under 35 USC §103(a) in view of Phillips et al. and Grove et al.

Claims 11, 13, 19, 21, 35 and 37 are rejected as allegedly being obvious in view of the article by Phillips et al. in combination with the article by Grove et al. This rejection is traversed.

In the rejection, it is argued that Phillips et al. disclose a treatment for AML using a combination of Cytarabine with Daunorubicin, an anthracycline. Further, the rejection argues that Grove et al. discloses in its abstract that (-)-L-OddC is the first L-nucleoside to have anticancer activity.

However, Grove et al. provides no suggestion that (-)-L-OddC is suitable for the treatment of AML. See, e.g., the tests results on cell lines set forth in table 1 of Grove et al., which are similar to the results set forth in Example 11 of WO '413 discussed above. Grove et al. state that AraC and (-)-OddC have similar activity against the CEM cell line, which the Examiner acknowledges is an acute lymphoblastic cell line. None of these cell lines mentioned Table 1 of Grove et al. appear to be an acute myelogenous leukemia cell line. As a result, Grove et al. provides no disclosure or suggestion that the compound, (-)-OddC is suitable for treating acute myelogenous leukemia. Thus, Grove et al. provide no motivation for modifying any treatment for AML possibly suggested by Phillips et al.

In view of the above remarks, it is respectfully submitted that Philips et al., taken alone or in combination with Grove et al., fails to render obvious applicants' claimed invention. Withdrawal of the rejection is respectfully requested.

Obviousness-type Double Patenting Rejection in view of Serial No. 10/853,241

Claims 11-13, 21, 34, 35, and 37 are rejected on grounds of obviousness-type double patenting in view of claims 24 and 26 of Serial No. 10/853,241. This rejection is traversed.

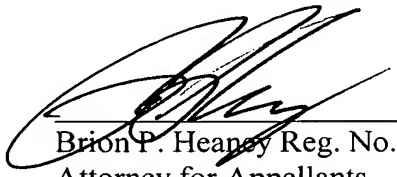
Claims 24 and 26 of Serial No. 10/853,241 broadly recite a further agent selected from two classes of agents, namely "a nucleoside analogue and/or a chemotherapeutic agent." The recitation of such classes does not render obvious the particular three component combination recited in applicants' claims. The rejection fails to set forth how the recitation of such a genus would lead one of ordinary skill in the art to select an embodiment in

accordance with applicants' claimed method.

Thus, since the rejection fails to establish how claims 24 and 26 render obvious applicants' claimed method, the obviousness-type double rejection is improper and should be withdrawn.

The Commissioner is hereby authorized to charge any fees associated with this response or credit any overpayment to Deposit Account No. 13-3402.

Respectfully submitted,



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